

Large-scale analysis yields new DNA regions involved in lung function

By Ernie Hood

A global consortium of researchers discovered six new loci - specific regions of the genetic code - that are associated with individual variations in an important clinical measure of lung function. The results were published [online](http://www.ncbi.nlm.nih.gov/pubmed/24929828) (<http://www.ncbi.nlm.nih.gov/pubmed/24929828>)

June 15 in the journal *Nature Genetics*. The findings point to previously unexplored pathways and mechanisms underlying lung function and could lead to the identification of novel therapeutic targets for lung diseases.

The scientists identified six genetic variants that appear to influence an individual's lung function, as determined by a widely used measurement called forced vital capacity (FVC). FVC is used to diagnose and monitor lung diseases.

Stephanie London, M.D., Dr.P.H., who heads both the NIEHS [Genetics, Environment, and Respiratory Disease Group](#) and [Genetic Epidemiology Group](#), was the senior author on the paper. She worked closely with others, including co-lead author Martin Tobin, Ph.D., from the University of Leicester in the U.K.; first author Daan Loth, Ph.D., from Erasmus University in the Netherlands; and a senior and junior lead author team from several countries.

The FVC research project was carried out at 134 centers in the U.S., Europe, Korea, and Australia. NIEHS research fellow Bonnie Joubert, Ph.D., and special volunteer Dana Hancock, Ph.D., were among the 160 authors credited in the paper.

Big science

Using a meta-analysis approach, the group analyzed the results of genome-wide association studies (GWAS) in 52,253 individuals from 26 countries. They followed up the FVC associations in 32,917 additional individuals of European descent.

The team found that the genes closest to the six loci they associated with FVC variation were expressed in lung tissue and in primary lung cells. The expression associations were confirmed in 762 whole blood samples, using a method known as expression quantitative trait locus analysis.

Long-term global collaboration

The FVC study builds upon previous work related to GWAS on lung function, conducted by London and her colleagues within the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) Consortium, a U.S.-based consortium in which London leads the pulmonary group, and SpiroMeta, a European-based consortium. That work resulted in papers in *Nature Genetics* in [2010](#) and [2011](#).

The six loci found in the current study were not identified in the previous GWAS, which found 27 loci associated with two other clinical measures of lung function, forced expiratory volume after one second (FEV1) and the ratio of FEV1 to FVC.

"These findings add important new knowledge to our previous work, by extending our grasp of the genetic factors that determine lung function," said London. "Characterizing these loci will help us understand their contribution to the risk of developing respiratory diseases, and the statistical power produced by the large sample size in these studies gives us confidence that our findings are on target, enabling us to gain new knowledge about the biology of these conditions."

The consortium has several ongoing and planned projects involving genetics of lung function, including studies of rare variants, ethnic differences, environmental interactions, and integrative genomics.

Citation: Loth DW, Artigas MS, Gharib SA, Wain LV, Franceschini N, Koch B, Pottinger TD, Smith AV, Duan Q, Oldmeadow C, Lee MK, Strachan DP, James AL, Huffman JE, Vitart V, Ramasamy A, Wareham NJ, Kaprio J, Wang XQ, Trochet H, Kahonen M, Flexeder C, Albrecht E, Lopez LM, de Jong K, Thyagarajan B, Alves AC, Enroth S, Omenaas E, Joshi PK, Fall T, Vinuela A, Launer LJ, Loehr LR, Fornage M, Li G, Wilk JB, Tang W, Manichaikul A, Lahousse L, Harris TB, North KE, Rudnicka AR, Hui J, Gu X, Lumley T, Wright AF, Hastie ND, Campbell S, Kumar R, Pin I, Scott RA, Pietilainen KH, Surakka I, Liu Y, Holliday EG, Schulz H, Heinrich J, Davies G, Vonk JM, Wojczynski M, Pouta A, Johansson A, Wild SH, Ingelsson E, Rivadeneira F, Volzke H, Hysi PG, Eiriksdottir G, Morrison AC, Rotter JI, Gao W, Postma DS, White WB, Rich SS, Hofman A, Aspelund T, Couper D, Smith LJ, Psaty BM, Lohman K, Burchard EG, Uitterlinden AG, Garcia M, Joubert BR, McArdle WL, Musk AB, Hansel N, Heckbert SR, Zgaga L, van Meurs JB, Navarro P, Rudan I, Oh YM, Redline S, Jarvis DL, Zhao JH, Rantanen T, O'Connor GT, Ripatti S, Scott RJ, Karrasch S, Grallert H, Gaddis NC, Starr JM, Wijmenga C, Minster RL, Lederer DJ, Pekkanen J, Gyllenstein U, Campbell H, Morris AP, Glaser S, Hammond CJ, Burkart KM, Beilby J, Kritchevsky SB, Gudnason V, Hancock DB, Williams OD, Polasek O, Zemunik T, Kolcic I, Petrini MF, Wjst M, Kim WJ, Porteous DJ, Scotland G, Smith BH, Viljanen A, Heliovaara M, Attia JR, Sayers I, Hampel R, Gieger C, Deary IJ, Boezen HM, Newman A, Jarvelin MR, Wilson JF, Lind L, Stricker BH, Teumer A, Spector TD, Melen E, Peters MJ, Lange LA, Barr RG, Bracke KR, Verhamme FM, Sung J, Hiemstra PS, Cassano PA, Sood A, Hayward C, Dupuis J, Hall IP, Brusselle GG, Tobin MD, London SJ.

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(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)



London holds a dual appointment at NIEHS, serving as head of the Genetics, Environment, and Respiratory Disease Group, as well as the Genetic Epidemiology Group. (Photo courtesy of Steve McCaw)



Joubert, a research fellow in the Genetics, Environment, and Respiratory Disease Group, received an NIH Fellows Award for Research Excellence in both 2013 and 2014. (Photo courtesy of Steve McCaw)



Hancock is particularly interested in the use of family-based samples to explore gene-environment interactions in complex respiratory diseases. (Photo courtesy of Steve McCaw)

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